Supplementary Materials and Methods

Extraction of Drug-induced rhabdomyolysis (DIR) related labeling

Drug labeling with keyword "rhabdomyolysis" was extracted by using full text search function in FDALabel public version (https://rm2.scinet.fda.gov/druglabel/#simsearch-0) (Data is acquired on December 9th, 2017). Thus, a total of 1,847 drug labeling with keyword "rhabdomyolysis" were obtained. Of 1847 drug labeling, 1580 drug labeling with single active ingredient were kept based on Unique Ingredient Identifier (UNII). Then, we only kept 1513 drug labeling administered through oral or parenteral route. Final, the latest version of drug labeling if multiple drug labeling exist with the same active ingredient, which generated a 172-drug list for further DIR classification.

Processing of FDA Adverse Event Reporting System (FAERS) data

The FAERS case reports for 172 DIR drugs were queried with keywords "*drug name*" and "*rhabdomyolysis*" through PharmaPendium database (https://www.pharmapendium.com/#/faers/select) (Data is acquired on December 9th, 2017). The case report information included outcomes, gender, age, concomitant drugs, and interacting drugs. The odds ratio for the DIR drug was calculated based on the contingency table via the following equation:

Table 1 Contingency table for odds ratio calculation

	Rhabdomyolysis	Other ADRs
Current Drug	a	b
Other Drugs	c	d

$$\text{Odds Ratio} = \frac{a \times d}{b \times c},$$

where *a* and *b* represent the numbers of rhabdomyolysis cases and other ADR cases induced by the current drug, respectively. The symbols *c* and *d* represent the total numbers of rhabdomyolysis cases and other ADR cases induced by other drugs in FARES database, respectively. In current version, the total numbers of rhabdomyolysis cases and ADR cases reported in FARES database were 42,912 and 14,160,191, respectively.

The female/male sex ratio for each DIR drug was calculated. In this study, we used 1.5 as cut-off to identify the sex-biased DIR drugs. For age distribution, we divided the ages into 7 groups (0~1 month, 2 month~2 years, 3~11 years, 12~17 years, 18~39 years, 40~64 years, and >65 years). Then, we calculated the age distribution for each drug and then assigned drugs in the age group with most number of case reports. For clinical outcome, we counted how many drugs could cause hospitalization or death, without death or lack of information, respectively.

Web application

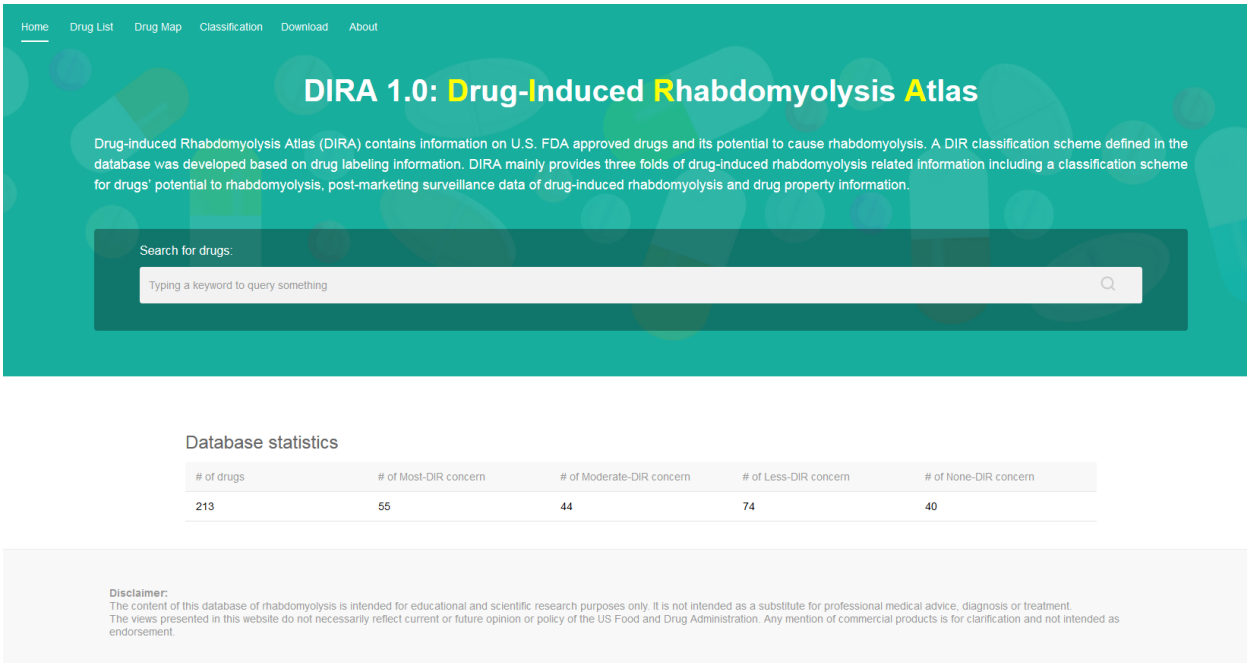

Figure 1 Web page of **D**rug-**I**nduced **R**habdomyolysis **A**tlas (DIRA)

Drug-**I**nduced **R**habdomyolysis **A**tlas (DIRA) is web-based application and under a Creative Commons Attribution-Noncommercial-Share Alike 4.0 License. For commercial use or customized versions, please contact biobyte solutions GmbH. DIRA provided "one-stop solution" on drug-induced rhabdomyolysis information including (1) a classification of 231 FDA approved drugs regarding their rhabdomyolysis potential; (2) post-marketing surveillance data from FAERS database; (3) drug properties information including daily dose, therapeutic categories, chemical structures, Chemical Abstracts Service (CAS) Registry Number, PubChem Compound Identifier, etc. Furthermore, DIRA is also linked to other popular pharmacology and biomedical related databases such as DrugBank (https://www.drugbank.ca/) [1],

PubChem (https://pubchem.ncbi.nlm.nih.gov/) [2], PharmGKB (https://www.pharmgkb.org/) [3], and DailyMed (https://dailymed.nlm.nih.gov/dailymed/). All the information is well-organized and downloadable. More importantly, labeling content of each DIR drug for making DIR concern call are listed and highlighted in the web application for further information and evaluation.

References

1 Wishart, D.S. et al. (2018) DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Research* 46 (D1), D1074-D1082

2 Kim, S. et al. (2016) PubChem Substance and Compound databases. *Nucleic Acids Research* 44 (Database issue), D1202-D1213

3 Hewett, M. et al. (2002) PharmGKB: the Pharmacogenetics Knowledge Base. *Nucleic Acids Research* 30 (1), 163-165